[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALLINCKRODT CHEMICAL WORKS]

Alkyl Carbonates in Synthetic Chemistry. I. Condensation with Organic Esters. Synthesis of Malonic Esters[1]

BY V. H. WALLINGFORD, AUGUST H. HOMEYER AND DAVID M. JONES

Compared to other simple organic esters, the alkyl carbonates have found little application in synthetic reactions. This is the first of several papers reporting investigations which greatly extend the uses of this interesting class of compounds. Scattered through the literature may be found a few instances in which alkyl carbonates have been employed but none of these suggests a type reaction of broad applicability or utility. The present paper describes a method of condensing alkyl carbonates with organic esters to produce malonic esters. The new synthesis of this important class of compounds is of considerable versatility and usefulness.

The earliest attempt to condense alkyl carbonates with esters was made by Wislicenus in 1887.[2] He reported that all attempts to condense diethyl carbonate with ethyl acetate failed and in a later paper[3] concluded that alkyl carbonates were not suitable for such "mixed acetoacetic ester" or Claisen type condensations. Many years later, however, Lux[4] succeeded in obtaining an 18% yield of diethyl malonate by slowly adding ethyl acetate to a refluxing mixture of benzene, diethyl carbonate and powdered sodium. Comparable results were obtained by Nelson and Cretcher,[5] who tried the reaction of diethyl carbonate with ethyl phenylacetate under various conditions, in alcohol, ether and benzene and with both sodium and sodamide. Condensation to diethyl phenylmalonate was effected only by means of sodium in ether and benzene, the latter medium giving a maximum of 20% yield. The principal side reaction was the condensation of ethyl phenylacetate with itself. Better yields in this same reaction were reported by Skinner,[6] who used potassium and sodium–potassium alloys as condensing agents in benzene as a solvent or reaction medium. The highest yield of ethyl phenylmalonate was 49% (based on the metal) when using 50% sodium–potassium alloy.

(1) Presented before the Division of Organic Chemistry at the St. Louis meeting of the American Chemical Society, April 8, 1941.
(2) Wislicenus, *Ber.*, **20**, 2930 (1887); *Ann.*, **246**, 313 (1888).
(3) Wislicenus, *Ber.*, **27**, 795 (1894).
(4) Lux, *ibid.*, **62**, 1827 (1929).
(5) Nelson and Cretcher, THIS JOURNAL, **50**, 2758 (1928).
(6) Skinner, *ibid.*, **59**, 322 (1937).

In the cases cited, a usual side reaction was the condensation of the ester with itself. Any procedure employing sodium or potassium metal suffers from the fact that these metals readily decompose alkyl carbonates. The use of a metal alcoholate in the presence of an alcohol may result in reversal of the desired condensation reaction. It was demonstrated by Cope and McElvain[7] and by Connor[8] that many substituted malonic esters undergo alcoholysis when heated in alcohol in the presence of sodium ethylate. For instance, in the case of diethyl phenylmalonate, cleavage occurs as shown in Equation 1.

$$C_6H_5CH(COOEt)_2 + EtOH \xrightarrow{NaOEt} C_6H_5CH_2COOEt + (EtO)_2CO \quad (1)$$

In many cases the products of the reaction, a substituted acetic ester and diethyl carbonate, were recovered and identified. Cope and McElvain recognized that this cleavage reaction was a reversal of the type of ester condensation which Lux had earlier applied in the synthesis of diethyl malonate from diethyl carbonate and ethyl acetate.

In the present investigation it has been demonstrated that the cleavage of diethyl phenylmalonate is reversible. By applying the principles of mass action, a procedure has been developed which gives a high yield of diethyl phenylmalonate from ethyl phenylacetate and diethyl carbonate. The same general method is applicable to the condensation of alkyl carbonates with a variety of esters, forming in each case the corresponding malonic ester. The general reaction may be written as in Equation (2)

$$R'CH_2COOR + (RO)_2CO + MOR \longrightarrow [R'C(COOR)_2]M + 2ROH \quad (2)$$

The essentials of the new procedure are (1) the use of an excess of the alkyl carbonate as a reaction medium or solvent, and (2) the removal of alcohol from the reaction mixture by distillation. It is clear from Equation (2) that these conditions favor the desired products by the effect of mass action. The idea of forcing an ester condensation reaction to completion by distilling off alcohol,

(7) Cope and McElvain, *ibid.*, **54**, 4319 (1932).
(8) Connor, *ibid.*, **55**, 4597 (1933).

one of the products of the reaction, has been applied by McElvain and others.[9]

The significance of the prescribed conditions for the reaction may be illustrated by the case of ethyl phenylacetate. Nelson and Cretcher[5] have shown that ethyl phenylacetate and diethyl carbonate do not condense in an alcoholic solution of sodium ethylate. This agrees with the observation of Connor[8] that diethyl phenylmalonate is cleaved by sodium ethylate in alcoholic solution to diethyl carbonate and ethyl phenylacetate. In the present investigation it was found that the reaction of equimolar amounts of ethyl phenylacetate and alcohol-free sodium methylate in an excess of diethyl carbonate, without removing alcohol by distillation, resulted in a yield of mixed esters of phenylmalonic acid amounting to 57% of the theoretical. Employing sodium ethylate and forcing the condensation to completion by distilling alcohol from the mixture, the yield of diethyl phenylmalonate was raised to 86%. Even in cases not clearly shown to be reversible, the conditions of our procedure favor the rapid completion of the reaction in the desired direction.

In the carbalkoxylation of some of the lower aliphatic esters there occurs simultaneously an appreciable amount of alkylation by the alkyl carbonate. For instance, in the condensation of diethyl carbonate with ethyl *n*-butyrate there was isolated along with the expected diethyl ethylmalonate a considerable amount of diethyl diethylmalonate. This was shown to be due to the alkylating action of diethyl carbonate upon the sodio-derivative of diethyl ethylmalonate which illustrates a similarity between alkyl carbonates and the esters of inorganic acids. This interesting alkylating action of alkyl carbonates is being studied further.

It may be pointed out that the product of the condensation reaction is in the form of a metal derivative which may be subjected to further reactions such as alkylation or acylation without separating it from the mixture. In fact, the authors have found that alkyl carbonates have many advantages as media for metalation, alkylation and other substitution reactions of organic compounds. Further papers on these subjects are in preparation.

(9) McElvain, THIS JOURNAL, **51**, 3124(1929); Briese and McElvain, *ibid*, **55**, 1697 (1933); Backhaus, U. S. Patent 1,425,626 (1922); Carter, U. S. Patent 1,472,324 (1923); reissue, U. S. Patent 16,591 (1927); Halbig and Kaufler, U. S. Patent 1,805,281 (1931).

Although the carbalkoxyl group is introduced most readily into aryl substituted acetic esters, the reaction has been successfully applied to a series of aliphatic esters up to ethyl stearate with satisfactory yields. The reaction has been limited to esters containing two hydrogen atoms in the alpha position. Ethyl α-phenylbutyrate and ethyl diethylacetate have so far failed to react. Simple branching of the chain on the beta carbon atom as in ethyl isovalerate does not prevent carbalkoxylation but if the beta carbon is tertiary as in ethyl *t*-butylacetate the yield is low. The reaction has been successful with a variety of carbonates.

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Experimental

Apparatus.—The apparatus consisted of a 3-necked flask of suitable size heated by an oil-bath and fitted to an electrically heated column of the total condensation, controllable take-off type. The column was 13 mm. inside diameter and packed throughout a length of 40 cm. with glass helices and connected to a suitable receiver and adjustable vacuum source. In one of the side-necks of the flask was inserted a motor driven stirrer constructed of piano wire. The other side-neck was fitted with a thermometer and dropping funnel. Agitation facilitates ebullition and aids in maintaining uniform column conditions.

The piano wire stirrer has been found very useful in this Laboratory not only for the condensation reactions but also to reduce superheating and bumping during vacuum distillation of the products. It was constructed by boring two-thirds through a rubber stopper with a cork borer 6–8 mm. in diameter, withdrawing the center portion and cutting it off. The stirrer was fashioned in the form of a long loop from piano wire (0.037″ diam.) and the shaft was forced through the rubber stopper from the bottom. A few drops of glycerol or castor oil placed in the well in the top of the rubber stopper lubricates the shaft. The loop-shaped agitator can be collapsed for insertion through a small side neck and the lower end of the loop may rotate against the bottom of the flask. The stopper may be bored and drilled at an angle if necessary. To prevent vibration the agitator shaft should not extend more than about 6 inches above the stopper for the size wire specified. Stirrers of this type have operated many hours continuously under vacuum with no sign of leakage of air, or seepage of lubricant.

General Procedure.—Equimolar ratios of the ester and sodium (or potassium) alcoholate were stirred and heated with an excess of alkyl carbonate (4–8 mols), and alcohol was removed from the reaction mixture by fractionation. The details of the condensation by two general procedures are illustrated in the following examples. The technique described in Method A has been employed for the carbalkoxylation of all esters listed in Table I. The technique described in Method B is applicable in most cases and is sometimes advantageous.

TABLE I

Starting material	Product	Yield, %	B. p., °C. (mm.) uncor.	n_D (t°C.)	M. p., °C. uncor.
Ethyl acetate[x]	Diethyl malonate[a]	25	100–105 (27)	1.4112 (25.5)	
	Tricarbethoxymethane	10	123 (6)		24–26
Ethyl butyrate	Diethyl ethylmalonate[b]	45	94–96 (13)	1.4170 (20)	
	Diethyl diethylmalonate[c]	10	105–107 (13)	1.4240 (20)	
Ethyl caproate	Diethyl butylmalonate	26	136–137 (21)	1.425 (20)	
	Diethyl ethylbutylmalonate[d]	34	122–124 (12)	1.428 (20)	
Ethyl isovalerate	Diethyl isopropylmalonate[e]	30	106–109 (18)	1.4188 (21.5)	
	Diethyl ethylisopropylmalonate[f]	10	114 (18)		
Ethyl isoamylacetate	Diethyl isoamylmalonate[g]	30			
	Diethyl ethylisoamylmalonate[h]	45	135 (16)	1.4292 (20)	
Ethyl laurate	Diethyl decylmalonate[i]	50	130–132 (1.5)	1.4341 (26)	
Butyl laurate[u]	Dibutyl decylmalonate	60	159–160 (1.5)	1.4390 (26.5)	
Ethyl stearate	Diethyl cetylmalonate[j]	50	185–190 (1)		
Butyl stearate[u]	Dibutyl cetylmalonate	55	206–215 (2)	1.4435 (26)	
Ethyl oleate[t]	Diethyl hexadecenylmalonate[k]		*ca.*–190 (1.5)	1.4511 (27)	
Ethyl malonate[r]	Tricarbethoxymethane	10	142–145 (17)	1.425 (24)	24–25
Ethyl sebacate[s]	1,1,8-Tricarbethoxyoctane[l]	60	185–198 (1.5)	1.444 (21)	
Methyl phenylacetate[x]	Dimethyl phenylmalonate	56	120–130 (3)		47–48
Ethyl phenylacetate[w]	Diethyl phenylmalonate	86	129 (2)		16–17
Propyl phenylacetate[q,v]	Dipropyl phenylmalonate	58	146–148 (4)		
Ethyl *p*-methylphenylacetate	Diethyl *p*-methylphenylmalonate[m]	65	124–125 (1)	1.4928 (20)	
Ethyl *p*-iodophenylacetate	Diethyl *p*-iodophenylmalonate[n]	60	165 (1.5)	1.5436 (20)	
Ethyl homoveratrate	Diethyl 3,4-dimethoxyphenylmalonate[o]	68	170 (1)	1.5076 (20)	
Ethyl β-phenylpropionate	Diethyl benzylmalonate[p]	67	105–108 (1)	1.484 (26.5)	
Ethyl 1-naphthaleneacetate	Diethyl 1-naphthalenemalonate	67			62–63

[a] Malondiamide, m. p. 174–175°. [b] Ethylmalonic acid, m. p. 111–113°. [c] Diethylmalonic acid, m. p. 126–128°. [d] Ethylbutylmalonic acid, m. p. 116–118°. [e] Isopropylmalonic acid, m. p. 88–90°. [f] Ethylisopropylmalonic acid, m. p. 132–134°. [g] Isoamylmalonic acid, m. p. 100–102°. [h] Ethylisoamylmalonic acid, m. p. 120–121°. [i] Decylmalonic acid, m. p. 118–119.5°; neutral equivalent found, 122.2. [j] Cetylmalonic acid, m. p. 117–120°; bromocetylmalonic acid, m. p. 93–94°. [k] The product was not pure; saponification equivalent calcd. 191, found 210. [l] Saponification equivalent found, 111.4; calcd. 110. [m] *p*-Methylphenylmalonic acid, m. p. 142–143°. [n] *Anal.* Calcd. for $C_{13}H_{15}O_4I$: C, 43.1; H, 4.1; I, 35.0. Found: C, 42.8; H, 4.1; I, 33.8. [o] *Anal.* Calcd. for $C_{15}H_{20}O_6$: C, 60.8; H, 6.7. Found: C, 60.9; H, 6.9. [p] Benzylmalondiamide, m. p. 229–230°. [q] Prepared from phenylacetyl chloride and *n*-propanol; b. p. 101–104° (4 mm.), $n^{28}D$ 1.4880, f. p. −35°. [r] The ethoxy-magnesium derivative of diethyl malonate was prepared, diethyl carbonate was added, and the experiment was continued as in method A. [s] Two moles of sodium ethylate per mole of ethyl sebacate were used, but only one appeared to react. [t] The ester was not pure; saponification equivalent calcd. 310, found 327. [u] Potassium butylate used and butyl alcohol distilled at 40–50 mm. pressure. [v] Potassium propylate used and propyl alcohol distilled at 100 mm. pressure. [w] See experimental part, Method B. [x] Alcohol free sodium alcoholate was used and the reaction mixture was refluxed at atmospheric pressure.

It may be desirable in certain cases to select the alkyl carbonate so that the products of the reaction can be readily separated by distillation. The esterifying alcohol of the ester and of the carbonate should be the same as the alcohol used to prepare the metal alcoholate. If the groups are not the same ester interchange may result in mixed products.

The results obtained with twenty esters are summarized in Table I. Conditions for obtaining optimum yields were not worked out in most cases. The yields are based on ester introduced as starting material and without allowance being made for recoverable unreacted ester.

Diethyl Decylmalonate. (Example of Method A.)—Sodium ethylate was made by dissolving sodium metal (7.5 g.) in anhydrous ethyl alcohol (150 ml.) and distilling the mixture to dryness at reduced pressure. After cooling, dry diethyl carbonate (300 ml.) and ethyl laurate (68 g.) were added. The reactants were stirred and refluxed under a packed column and alcohol was removed as distillate. At first, distillation was at 200 mm. pressure, and later at atmospheric pressure. When no more alcohol was obtainable as distillate, the reaction was considered complete. After cooling, the mixture was acidified with acetic acid (20 ml.), and shaken with water. The organic layer was washed, dried and distilled. After removing the diethyl carbonate the product distilled at 130–132° at 1.5 mm., $n^{26}D$ 1.4341. The yield was 45 g. (50%). The ester was hydrolyzed to decylmalonic acid which, crystallized from a mixture of chloroform and petroleum ether, melted at 118–119.5°; neutral equivalent calcd. for $C_{13}H_{24}O_4$, 122.1; found, 122.2.

Diethyl Phenylmalonate. (Example of Method B.)—Diethyl carbonate (600 ml.) and ethyl phenylacetate (123 g.) were placed in a 1-liter 3-necked flask of the apparatus described above and the mixture was stirred and heated to refluxing under a pressure of 125 mm.[10] A solution of sodium ethylate, made from sodium (18 g.) and anhydrous ethyl alcohol (400 ml.), was added during six

(10) Atmospheric pressure and correspondingly higher temperatures were equally satisfactory.

hours from the dropping funnel. Alcohol was removed simultaneously from the head of the column at such a rate that it did not accumulate in the reaction mixture. When no more alcohol was obtained as distillate, the reaction mixture was cooled and poured on a mixture of ice and hydrochloric acid. The organic layer was separated, washed with water containing a little salt, dried over calcium chloride and fractionated until all the diethyl carbonate had been removed. The residue was distilled from a Claisen flask at reduced prssure: yield 152.5 g. (86%), m. p. 16–17°, b. p. 129–30° at 2 mm.

Summary

A procedure has been developed for condensing alkyl carbonates with organic esters by metal alcoholates for the convenient production of malonic esters. This has been applied to numerous aliphatic and aryl substituted aliphatic esters. In certain cases alkyl carbonates exhibit an alkylating action.

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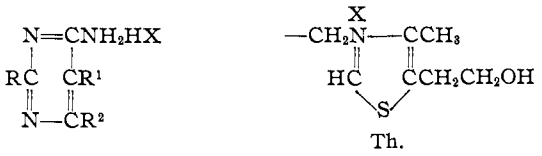
Some Analogs of Thiamin and their Physiological Activity[1]

BY GUSTAV A. STEIN, W. L. SAMPSON, J. K. CLINE AND JOSEPH R. STEVENS

The following analogs of thiamin, some of which have been credited with physiological activity, were prepared



I, R = H; R^1 = Th; R^2 = CH_3; X = Br (Makino vitamin); 6-methyl-5-thiazolium isomer (activity claimed)[2]

II, R = H; R^1 = CH_3; R^2 = Th; X = Br (reversed Makino); 5-methyl-6-thiazolium isomer

III, R = CH_3; R^1 = H; R^2 = Th; X = Br, 2-methyl-6-thiazolium isomer (activity claimed)[3]

IV, R = C_2H_5; R^1 = Th; R^2 = H; X = Br, 2-ethyl-5-thiazolium homolog

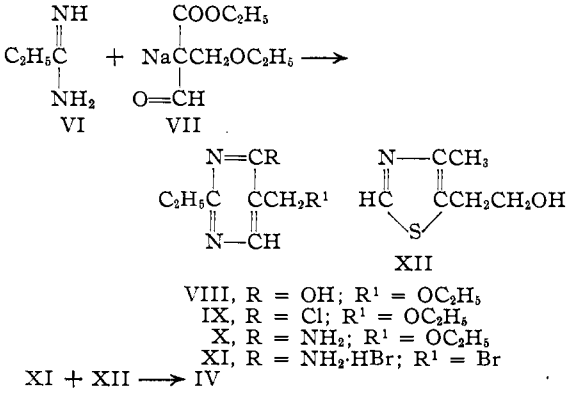
V, R = CH_3; R^1 = Th; R^2 = H; X = Cl, (thiamin)

The biological activity of these compounds was studied and compared with that of thiamin hydrochloride, V.

Discussion

Whereas compounds I, the so-called Makino vitamin, and III were prepared according to known methods,[2,3] the ethyl homolog IV was made by adapting the Williams and Cline[4] synthesis for the 2-methyl homolog, by condensing 2-ethyl-4-amino-5-bromomethylpyrimidine dihydrobromide, XI, with 4-methyl-5-(β-hydroxyethyl)-thiazole, XII. The synthesis of XI starts with the condensation of propionamidine, VI, with the sodium formyl derivative of γ-ethoxyacetoacetic ester, VII, to yield 2-ethyl-4-hydroxy-5-ethoxymethylpyrimidine, VIII, m. p. 146–146.5°. Upon chlorination with phosphorus oxychloride, III gave 2-ethyl-4-chloro-5-ethoxymethylpyrimidine, IX, which without further purification was aminated to yield 2-ethyl-4-amino-5-ethoxymethylpyrimidine, X, m. p. 64.5–65.5°. Treatment of X with glacial acetic hydrobromic acid yielded 2-ethyl-4-amino-5-bromomethylpyrimidine dihydrobromide, XI, m. p. (crude) 175–178°.

The above series of reactions may be represented by the following formulas



In a similar way the synthesis of the 2-methyl-6-thiazolium isomer, III, was tried as follows:

Condensing acetamidine, XIII, with ethyl γ-ethoxyacetoacetate, XIV, in the usual way, gave 2-methyl-5-hydroxy-6-ethoxymethylpyrimidine,[3] XV, which, on treatment with phosphorus oxy-

(1) This paper is No. XX in the R. R. Williams Vitamin B_1 Series (XIX, Joseph R. Stevens and Gustav A. Stein, THIS JOURNAL, **62**, 1045–1048 (1940)).

(2) H. Andersag and K. Westphal, "Über die Synthese des antineuritischen Vitamins," *Ber.*, **70**, 2035 (1937).

(3) British Patent 471,416 to I. G. Farbenindustrie A. G., accepted Aug. 30, 1937; French Patent 816,432 to I. G. Farbenindustrie A. G.; published August 7 (1937).

(4) R. R. Williams and J. K. Cline, THIS JOURNAL, **58**, 1504–1505 (1936).